Global Regulatory Policy

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: Docket No. 04D-0459
Draft Guidance, Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $3 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this draft guidance (hereafter referred to as the Guidance). Based on our experience in assessing the influence of pregnancy on pharmacokinetics and pharmacodynamics of drugs, we offer the following comments.

Merck supports the Agency's issuance of a Guidance for sponsors regarding the issues to be considered when designing and conducting pharmacokinetic studies in pregnant women. We appreciate the scope of the topics included; however, we are concerned with the logistics and feasibility of the recommendations, specifically how sponsors will do what is suggested.

'Centers of Excellence' to Conduct Clinical Studies in Pregnant Women

The participants in pharmacokinetic studies in a pregnant population appear to fit into two categories – studies that will enroll women with pre-existing or concurrent conditions that require treatment, and studies that will enroll pregnant volunteers who do not require therapy.

There are many phase 1 study sites that are highly experienced in the proper collection and storage of PK samples, but lack access to a pregnant population and are unable to follow women for longer periods (e.g. postpartum). Conversely, there are many phase 3 study sites that have access to study subjects who require treatment and can provide long-term follow-up, but lack the expertise to process PK samples. Ideally, the needs of pregnant women are best served by specialized study sites that are capable of the following. Merck would be highly interested in conducting studies at specialized sites that can:

- provide routine OB-GYN care as well as conduct clinical research,
- screen a large number of women, those who volunteer and those who require treatment,
- follow women before, during, and after pregnancy, and
- properly collect, handle, and store pharmacokinetic samples.

Recommendation: We encourage the Agency to support the establishment of 'centers of excellence' to provide sponsors with locations at which to conduct PK studies. The establishment of centers that specialize in studies of pregnant women will make it easier for sponsors to conduct successful studies in this population.

Obtaining Baseline Pharmacokinetics

There are two possible timeframes in which baseline pharmacokinetic values should be obtained, prior to pregnancy and postpartum. Both of these may be limited for practical reasons.

It is difficult to obtain baseline values prior to pregnancy as subjects would have to be consented prior to becoming pregnant and therefore, recruitment efforts would be directed to women trying to become pregnant who are also willing to participate in a clinical trial. It may be difficult to identify such subjects without involvement of a network of referring obstetricians or academic centers committed to such research. Typical Phase I study sites would likely not have such women in their databases and/or be equipped to follow subjects throughout their pregnancy and postpartum. See more on this topic under *'Centers of Excellence' to Conduct Clinical Studies in Pregnant Women*.

In the postpartum period, the Guidance recommends that baseline PK values be collected from women who elect not to breastfeed. Such samples may be collected around 3 months postpartum, after physiology returns to the prepregnancy state. Merck agrees with this. It is problematic to collect samples in women who choose to breastfeed, as the timing of the samples is widely variable (if the samples are taken at varied times after each woman discontinues breastfeeding) and to collect samples in women while lactating may confound interpretation of the data.

Recommendation: The Guidance should acknowledge the complexity of obtaining baseline values and provide for flexible trial designs. Sponsors should be permitted to design each protocol on a case-by-case basis, given the population, study objectives, and analysis plan.

Investigator-Defined Windows for PK/PD Assessments During a Given Trimester

In Section IV. A. Longitudinal Studies, the Guidance suggests that because many changes occur within a given trimester, assessments should be obtained within a narrow window of time (e.g., a 4-week window per trimester). However, PK and PD results may differ depending upon when the window occurs in a given trimester (physiologically, one is different at the beginning of the 2nd trimester than at the end). Moreover, if different investigators obtain assessments in different windows of time, it will be difficult to compare across studies.

Recommendation: The use of a population PK approach may be helpful since the week of pregnancy can be used as a covariate in the analysis. An alternative is to standardize when assessments should be obtained (e.g., the last 2 to 3 weeks of a given trimester).

Comparison Between Single-Dose Postpartum PK and Multiple-Dose Pregnancy PK

In Section V.B., the Guidance states that if PK is linear, single-dose postpartum data can be compared to multiple-dose data during pregnancy. Although PK maybe linear prior to pregnancy and postpartum, it is possible that PK is not linear during pregnancy and therefore, these comparisons may not be valid. In addition, it is noted that PK may change in weeks to months postpartum and therefore, different drugs may require a different amount of time to return to linear kinetics.

Recommendation: We request that the Agency clarify the basis upon which comparisons can be made. The PK of a particular drug in women prior to pregnancy, during pregnancy, and postpartum should be established. We cannot assume that a drug has linear kinetics at all time-points as physiology changes. Only after the PK is deemed to be linear at all times can the comparison between single-dose postpartum PK be made to multiple-dose pregnancy PK.

Concentration of Drug Excreted in Human Breast Milk

Sponsors are frequently asked by healthcare providers and consumers for information regarding the concentration of drug excreted in human breast milk so that consumers may utilize this information when making decisions about whether to continue to breastfeed while taking medication. It is difficult for women to make this decision based on drug concentrations in animals alone (e.g. rat).

Recommendation: The Guidance makes no mention of gathering this information. Mention of this topic by way of Guidance may encourage sponsors to assess the concentration of drug excreted in human breast milk.

In conclusion, while this Guidance provides a general framework of the issues to consider when designing and conducting PK and PD studies in pregnant women, the Guidance could be strengthened by:

- establishing 'centers of excellence' to provide sponsors with locations at which to conduct PK studies
- providing for flexible trial designs
- using a population PK approach, including the week of pregnancy as a covariate in the analysis
- clarifying the basis upon which PK comparisons can be made prior to pregnancy, during pregnancy, and postpartum
- addressing the concentration of drug excreted in human breast milk in the Guidance.

Please feel free to contact me with any questions at 301-941-1403

Sincerely,

Lauren M Hetrick

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